

About XARELTO® (rivaroxaban) in Reducing the Risk of Stroke in Patients with Atrial Fibrillation

FAST FACTS

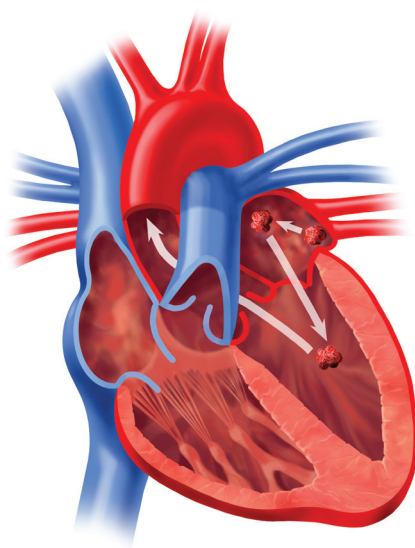
- ◆ XARELTO® is a once-daily, oral anti-coagulant approved in the United States by the U.S. Food and Drug Administration (FDA) to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AFib). There are limited data on the relative effectiveness of XARELTO® and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled
- ◆ AFib is a common condition in the heart that causes the atria – the upper two chambers of the heart – to beat very fast and irregularly. When this happens, blood isn't pumped through the heart as well as it should be, which makes people with AFib vulnerable to the formation of a blood clot in the atria¹
- ◆ If the blood clot breaks off and travels to the brain, it can cause a stroke¹
- ◆ Patients with AFib are at a five-fold increased risk for stroke compared with the general population²

About AFib

The heart consists of four chambers: two upper chambers (atria) and two lower chambers (ventricles). A healthy heart pumps blood from its chambers through the bloodstream at a regular and constant rate, allowing oxygenated blood to circulate through the body. This pumping action is controlled by coordinated electrical signals in the heart.¹

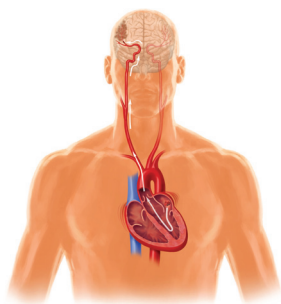
AFib is the most common cardiac rhythm disorder that causes the atria to beat very fast and irregularly. When this happens, blood isn't pumped into the ventricles as well as it should be. AFib may also impact the amount of blood pumped out of the ventricles to the body.

AFib can produce a broad range of symptoms. Because it is characterized by an irregular and fast pulse, patients sometimes experience unpleasant palpitations or discomfort in the chest. In addition, the reduced pumping ability of the heart may cause weakness, faintness, and shortness of breath. In more severe cases chronic fatigue, chest pain (angina), or stroke may occur.¹ Some patients may experience no symptoms at all.



Because the heart's atria are not contracting properly, blood can pool in the heart's upper chambers, which may lead to the formation of blood clots within the atria. If these clots break away, they can be carried to the brain, potentially resulting in a stroke.¹

The link between AFib and stroke



AFib increases a patient's risk for stroke five-fold, causing about 70,000 strokes annually in the United States alone.^{1,2}

The effects of stroke vary from person to person based on the type, severity, and time to treatment. For those who

suffer non-fatal strokes, disabilities can include paralysis, vision difficulties, speech problems and memory loss.³

Causes and risk factors of AFib

AFib may occur even when there are no other signs of a heart disorder. Abnormalities or damages to the heart's structure are the most common cause of AFib. Other possible causes include:^{1,4}

- ◆ High blood pressure
- ◆ Heart attack
- ◆ Congenital heart defects
- ◆ An overactive thyroid or other metabolic imbalance
- ◆ Lung diseases
- ◆ Rheumatic heart disease
- ◆ Sleep apnea

Age is a major risk factor for AFib. The median age of people with AFib is about 75, and approximately 70 percent are between 65 and 85 years of age.⁵ Other risk factors that increase risk of stroke in people with AFib include high blood pressure, heart failure, diabetes, and prior stroke.⁵

Prevalence of AFib and stroke

AFib is the most common cardiac rhythm disorder, affecting more than 2.2 million people in the U.S.⁴

In the past 20 years, there has been a 66 percent increase in hospital admissions for AFib, which has been attributed to the aging population, a rising prevalence of heart disease, and more frequent diagnosis.¹ Looking ahead,

it is estimated that AFib will affect more than 12 million people in the U.S. by 2050.²

Worldwide, stroke is responsible for five million deaths each year.⁶ Stroke affects approximately 795,000 individuals annually in the U.S. (approximately one person every 40 seconds).² More than four million people in the U.S. have survived a stroke or brain attack and are living with the after-effects. At least 15-20 percent of all strokes occur in patients with AFib.¹

Several factors are considered when assessing the risk of a stroke for a patient with AFib. Patients who have had a prior stroke, transient ischemic attack (TIA), or non-CNS systemic embolism are at high risk. Additional factors that increase risk of stroke in patients with AFib include high blood pressure, heart failure, diabetes mellitus or being 75 or older.^{2,4}

Reducing the risk of stroke in patients with AFib

Primary treatment for AFib aims to restore normal heart rate. Given the elevated risk of stroke among patients with AFib, medications to help reduce the risk of stroke also are frequently administered.⁷

Guidelines from the American College of Cardiology, American Heart Association and European Society of Cardiology recommend that patients with AFib over 65 with risk factors including diabetes, coronary artery disease, hypertension, recent heart failure and thromboembolism, receive preventive oral anticoagulation therapy.⁵ In practice, studies show that nearly half of patients with AFib do not receive appropriate preventive medication to help protect against the risk of stroke.⁸⁻¹¹

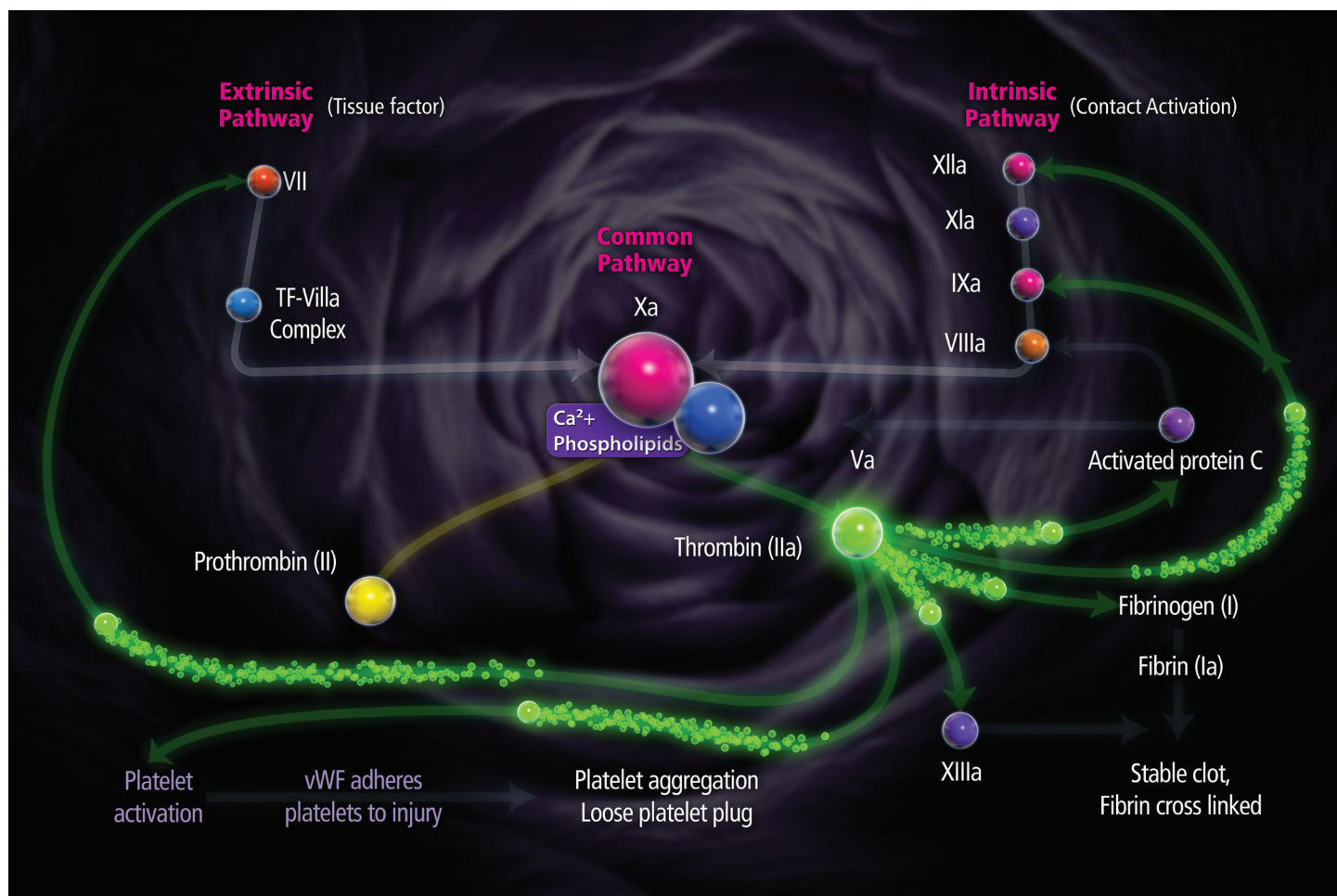
XARELTO® is a once-daily, oral anticoagulant approved in the United States by the FDA to reduce the risk of stroke and systemic embolism in patients with nonvalvular AFib. There are limited data on the relative effectiveness of XARELTO® and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled.



How XARELTO® works

XARELTO® is a Factor Xa inhibitor.¹² Factor Xa has emerged as a target for new anticoagulants due to its pivotal role in the coagulation cascade where it stimulates the production of thrombin, the enzyme that promotes clot formation.^{12,13}

Factor Xa regulates thrombin generation, instead of inhibiting the action of thrombin, which may allow for other coagulation processes to continue.¹⁴ Selective inhibition of Factor Xa is expected to help modulate the formation of the prothrombinase complex to reduce the so-called “thrombin burst.”^{13,14}



By selectively binding to Factor Xa, rivaroxaban inhibits the conversion of prothrombin to thrombin

Important Safety Information

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT XARELTO®?

For people taking XARELTO® for atrial fibrillation:

People with atrial fibrillation (an irregular heart beat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. XARELTO® lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking XARELTO®, you may have an increased risk of forming a clot in your blood.

♦ **Do not stop taking XARELTO® without talking to the doctor who prescribes it for you. Stopping XARELTO® increases your risk of having a stroke or forming blood clots in other parts of your body.**

If you have to stop taking XARELTO®, your doctor may prescribe another blood thinner medicine to prevent a blood clot from forming.

For all people taking XARELTO®:

♦ XARELTO® can cause bleeding which can be serious, and rarely may lead to death. This is because XARELTO® is a blood thinner that reduces blood clotting. While you take XARELTO® you are likely to bruise more easily and it may take longer for bleeding to stop.

You may have a higher risk of bleeding if you take XARELTO® and take other medicines that increase your risk of bleeding including:

- aspirin or aspirin containing products,
- non-steroidal anti-inflammatory drugs (NSAIDs)
- warfarin sodium (Coumadin®, Jantoven®)
- any medicine that contains heparin
- clopidogrel (Plavix®)
- prasugrel (Effient®)
- ticagrelor (Brilinta®)

Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

Call your doctor or get medical help right away if you develop any of these signs or symptoms of bleeding:

- ♦ tingling, numbness or muscle weakness, especially in your legs. This is particularly important if you had a procedure called spinal or epidural puncture as part of your anesthesia during surgery.
- ♦ any unexpected bleeding, or bleeding that lasts a long time (such as nose bleeds that happen often, unusual bleeding from gums, or menstrual bleeding that is heavier than normal or vaginal bleeding)

- ♦ bleeding that is severe or that you cannot control
- ♦ red, pink or brown urine
- ♦ bright red or black stools (look like tar)
- ♦ cough up blood or blood clots
- ♦ vomit blood or your vomit looks like “coffee grounds”
- ♦ headaches, feeling dizzy or weak
- ♦ pain, swelling, or new drainage at wound sites

WHO SHOULD NOT TAKE XARELTO®?

Do not take XARELTO® if you:

- ♦ currently have abnormal or unusual bleeding
- ♦ are allergic to rivaroxaban or any of the ingredients of XARELTO®

WHAT SHOULD I TELL MY DOCTOR BEFORE OR WHILE TAKING XARELTO®?

Before taking XARELTO® tell your doctor if you:

- ♦ Have ever had bleeding problems
- ♦ Have liver or kidney problems
- ♦ Have any other medical condition
- ♦ Are pregnant or planning to become pregnant
- ♦ Are breastfeeding or plan to breastfeed

Tell all of your doctors and dentists that you are taking XARELTO®. They should talk to the doctor who prescribed XARELTO® for you before you have any surgery, medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way XARELTO® works. Certain medicines may increase your risk of bleeding.

Especially tell your doctor if you take:

- ♦ ketoconazole (Nizoral®)
- ♦ itraconazole (Onmel™, Sporanox®)
- ♦ ritonavir (Norvir®)
- ♦ lopinavir/ritonavir (Kaletra®)
- ♦ indinavir (Crixivan®)
- ♦ carbamazepine (Carbatrol®, Equetro®, Tegretol®, Tegretol®-XR, Teril™, Eptol®)
- ♦ phenytoin (Dilantin-125®, Dilantin®, Phenobarbital, Solfoton™)
- ♦ rifampin (Rifater®, Rifamate®, Rimactane®, Rifadin®)
- ♦ St. John’s wort (Hypericum perforatum)

Ask your doctor if you are not sure if your medicine is one listed above. Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.



HOW SHOULD I TAKE XARELTO®?

Take XARELTO® exactly as prescribed by your doctor. **Do not change your dose or stop taking XARELTO® unless your doctor tells you to.**

For people who have:

- ♦ **atrial fibrillation:** Take XARELTO® 1 time a day **with your evening meal. Stopping XARELTO® may increase your risk of having a stroke or forming blood clots in other parts of your body.**
- ♦ **hip or knee replacement surgery:** Take XARELTO® 1 time a day **with or without food.**

Your doctor may stop XARELTO® for a short time before any surgery, medical or dental procedure. Your doctor will tell you when to start taking XARELTO® again after your surgery or procedure.

Do not run out of XARELTO®. Refill your prescription for XARELTO® before you run out. When leaving the hospital following a hip or knee replacement, be sure that you will have XARELTO® available to avoid missing any doses.

If you miss a dose of XARELTO®, take it as soon as you remember on the same day.

If you take too much XARELTO®, go to the nearest hospital emergency room or call your doctor right away.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF XARELTO®?

XARELTO® can cause bleeding which can be serious, and rarely may lead to death. *Please see "What is the most important information I should know about XARELTO®?"*

Tell your doctor if you have any side effect that bothers you or that does not go away.

Discuss any side effects with your doctor. You are also encouraged to report side effects to the FDA: visit <http://www.fda.gov/medwatch> or call 1-800-FDA-1088. You may also report side effects to Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (526-7736).

Please see full **Product Information**, including **Medication Guide**.

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References:

1. American College of Cardiology: CardioSmart. Atrial Fibrillation. Available at: <http://www.cardiosmart.org/HeartDisease/CTT.aspx?id=222>. Accessed May 24, 2011.
2. Roger V, Go A, Lloyd-Jones D, et al. Heart Disease and Stroke Statistics--2011 Update: A Report From the American Heart Association. *Circulation*. 2011; 123:e18-e209.
3. American Stroke Association. Effects of stroke. http://www.strokeassociation.org/STROKEORG/AboutStroke/EffectsofStroke/Effects-of-Stroke_UCM_308534_SubHomePage.jsp. Accessed September 29, 2011.
4. Kannel WB, Benjamin EJ. *Med Clin North Am*. 2008; 92:17-40.
5. Fuster V, Lars ER, Cannom DS, et al. 2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC Practice Guidelines for the Management of Patients with Atrial Fibrillation, *Circulation*. 2011, 123:e269-e367.
6. World Health Organization. The Atlas of Heart Disease and Stroke. 2010. http://www.who.int/cardiovascular_diseases/resources/atlas/en/. Accessed May 24, 2011.
7. American College of Cardiology: CardioSmart. Guideline: Atrial Fibrillation. Available at: <http://www.cardiosmart.org/ManageCondition/Default.aspx?id=892>. Accessed May 24, 2011.
8. Lakshminarayan K, Solid CA, Collins AJ, Anderson DC, Herzog CA. Atrial fibrillation and stroke in the general Medicare population: a 10-year perspective (1992 to 2002). *Stroke*. 2006;37(8):1969-1974. doi:10.1161/01.STR.0000230607.07928.17.
9. Waldo AL, Becker RC, Tapson VF, Colgan KJ; for the NABOR Steering Committee. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. *J Am Coll Cardiol*. 2005;46(9):1729-1736. doi:10.1016/j.jacc.2005.06.077.
10. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GYW. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med*. 2010;123(7):638-645. doi:10.1016/j.amjmed.2009.11.025.
11. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Ann Intern Med*. 1999;131(12):927-934.
12. Perzborn E, Strassburger J, Wilmen A, et al. In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939 – an oral, direct Factor Xa inhibitor. *J Thromb Haemost* 2005; 3: 514-521.
13. Turpie AG. Oral, direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. *Arterioscler Thromb Vasc Biol* 2007; 27:1238-1247.
14. Hoffman M, Monroe DM. Coagulation 2006: a modern view of hemostasis. *Hematol Oncol Clin North Am*. 2007; 21(1):1-11.